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Results of a Multicenter Phase II Trial of Brentuximab Vedotin as Second-Line Therapy before Autologous Transplantation in Relapsed/Refractory Hodgkin Lymphoma

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A B S T R A C T

This multicenter prospective phase II study examines the activity and tolerability of brentuximab vedotin as second-line therapy in patients with Hodgkin lymphoma that was relapsed or refractory after induction therapy. Brentuximab vedotin (1.8 mg/kg) was administered i.v. on day 1 of a 21-day cycle for a total of 4 cycles. Patients then proceeded to autologous hematopoietic cell transplantation (AHCT), if eligible, with or without additional salvage therapy, based on remission status after brentuximab vedotin. The primary endpoint was overall response rate (ORR). Secondary endpoints were safety, stem cell mobilization/collection, AHCT outcomes, and association of $CD68^+$ with outcomes. Of 37 patients, the ORR was 68% (13 complete remission, 12 partial remission). The regimen was well tolerated with few grade 3/4 adverse events, including lymphopenia (1), neutropenia (3), rash (2), and hyperuricemia (1). Thirty-two patients (86%) were able to proceed to AHCT, with 24 patients (65%) in complete remission at time of AHCT. Thirteen patients in complete remission, 4 in partial remission, and 1 with stable disease (49%) received AHCT without salvage combination chemotherapy. CD68 expression did not correlate with response to brentuximab vedotin. The median number of stem cells mobilized was 6.0×10^6 (range, 2.6 to 34), and median number of days to obtain minimum collection (2×10^6) was 2 (range, 1 to 6). Brentuximab vedotin as second-line therapy is active, well tolerated, and allows adequate stem cell collection and engraftment. For Hodgkin lymphoma patients with relapsed/refractory disease after induction therapy, second-line brentuximab vedotin, followed by combination chemotherapy for residual disease, can effectively bridge patients to AHCT.

INTRODUCTION

Up to 30% of patients with Hodgkin lymphoma (HL) will relapse or are refractory to primary induction chemotherapy [1,2]. Standard second-line therapies for these patients include combination chemotherapy regimens such as ICE (ifosfamide, carboplatin, etoposide), DHAP (dexamethasone, high dose cytarabine, cisplatin), or GDP (gemcitabine, dexamethasone, cisplatin), which typically yield responses rates of about 60% to 80% but can have significant myelosuppression, including grade 3/4 thrombocytopenia, febrile neutropenia, and grade 3/4 anemia. Up to 60% of patients may require packed RBC transfusion, and 30% may require platelet transfusion. Combination chemotherapies may also impair the ability to successfully mobilize stem cells (14%) for autologous hematopoietic cell transplantation (AHCT) [3-7]. Alternative salvage strategies with fewer hematologic adverse effects would be advantageous to patients destined for AHCT.

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Brentuximab vedotin is an antibody–drug conjugate linking an anti-CD30 antibody to the microtubule-disrupting agent, monomethyl auristatin E [8]. It selectively induces apoptosis in CD30-expressing cells while sparing toxicity to off-target tissues [9]. Based on a phase II trial demonstrating an overall response rate (ORR) of 75% with a tolerable safety profile, the US Food and Drug Administration approved brentuximab vedotin for use in patients with HL who have received at least 2 prior lines of therapy [10,11]. We expect that brentuximab vedotin as second-line treatment will also be efficacious and tolerable. Previously, we demonstrated that brentuximab vedotin can act as an effective bridge to allogeneic transplantation [12,13]. We now hypothesize that brentuximab vedotin as a second-line treatment can be an effective bridge to autologous transplantation with no deleterious effects on stem cell mobilization or engraftment.

METHODS

This is a multicenter, investigator-initiated, phase II clinical trial performed at City of Hope and Weill Cornell Medical College. This trial was registered with clinicaltrials.gov (NCT01393717) and approved by both institutional review boards, and an assurance was filed with the US Department of Health and Human Services. Informed consent was obtained for all study participants in compliance with the Declaration of Helsinki.

Patient Eligibility

Patients over age 10 years with histologically confirmed $CD30^+$ relapsed/refractory classical HL were eligible. All patients had biopsy-proven relapsed/refractory HL after induction therapy with ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine), BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone), or a combination ± consolidative radiotherapy. Pediatric patients may have received ABVE-PC (doxorubicin, bleomycin, vinblastine, etoposide, prednisone, cyclophosphamide). Patients were ineligible if they had received any second-line therapy chemotherapy. Patients were required to show radiographically measureable disease and standard organ functions.

Treatment Plan

Treatment consisted of 1.8 mg/kg brentuximab vedotin i.v. every 3 weeks for a maximum of 4 cycles. Figure 1 shows the treatment schema. One cycle of therapy was defined as the 21 days after i.v. administration of brentuximab vedotin. Patients with complete remission (CR), partial remission (PR), or stable disease (SD) at the end of 2 cycles were permitted to continue brentuximab vedotin for 2 more cycles. Patients who achieved CR or PR were allowed to proceed to AHCT directly. Patients who achieved PR had the option of receiving additional combination chemotherapy before AHCT. Patients with SD or progressive disease (PD) were required to undergo salvage chemotherapy before AHCT. The choice of combination chemotherapy regimen was at the discretion of the treating physician. For stem cell mobilization most patients received cyclophosphamide (1.5 g/m^2) and granulocyte colony-stimulating factor (G-CSF; 10 μg/kg) as priming agents, but for slow collectors ($<1.0 \times 10^6$ $CD34^+$ cells first day) plerixafor was added per City of Hope standard operating procedures.

Study Design and Statistical Methods

The primary objective was to evaluate the antitumor activity of brentuximab vedotin as second-line therapy. The primary endpoint was the best ORR (CR plus PR) per 2007 Cheson criteria [14]. Responses were assessed at end of cycles 2 and 4. All CRs were confirmed by fluorodeoxyglucose positron emission tomography evaluation with the standardized uptake value (SUV) to be below the background of the mediastinal blood pool. Secondary endpoints were toxicity, stem cell mobilization, and engraftment. Based on historical data with standard chemotherapy regimens, we considered a response rate of at least 60% to be sufficient to warrant further evaluation. A Simon 1-stage design with a 1-sided alpha of 5% and 80% power was used to assess ORR. In the first stage 23 patients were enrolled, with the design specifying that if 12 or more patients achieved CR or PR, accrual would continue to a total of 37 patients, with 23 or more responses regarded as evidence of sufficient activity to warrant further investigation. Toxicity was assessed every cycle and graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 [15].

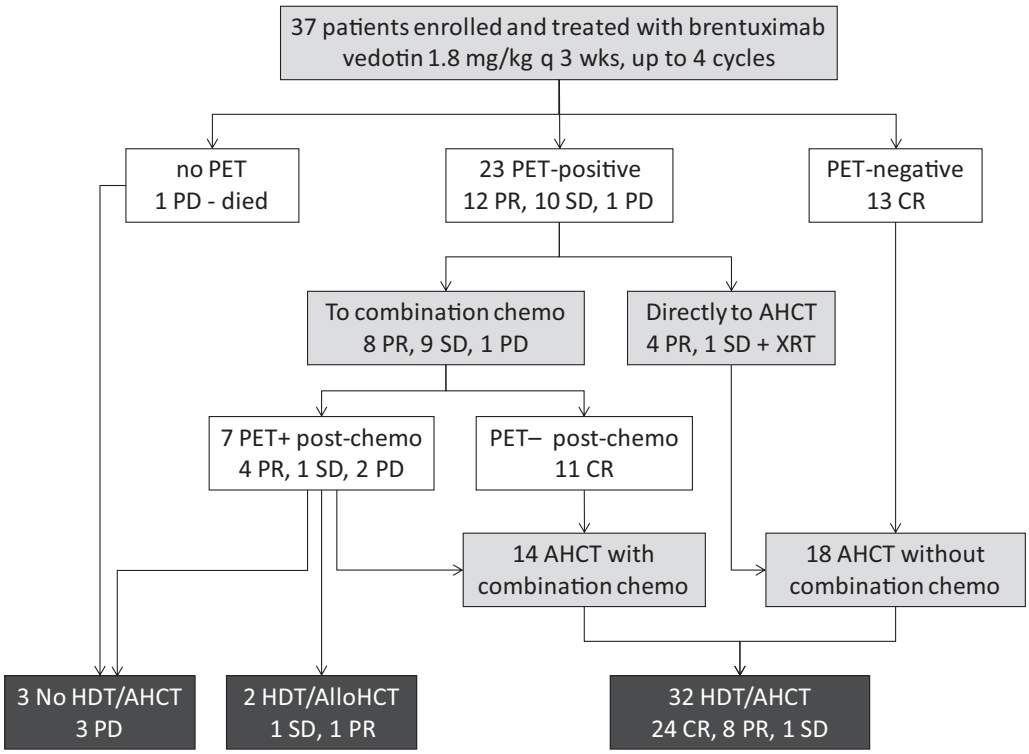

Figure 1. Study schema. Patients with relapsed/refractory HL were treated with brentuximab vedotin 1.8 mg/kg i.v. every 3 weeks for maximum of 4 cycles. Radiographic assessment was done at the end of cycle 2 with computed tomography (CT) or CT/positron emission tomography (PET) scan. Patients were allowed to continue the study if they achieved CR/PR/SD after 2 cycles. Radiographic assessment at the end of the study was done with CT/PET scan. Patients who achieved CR went directly to AHCT. Patients who achieved PR had the option of going directly to AHCT or receiving other salvage chemotherapy by investigators choice. XRT indicates local radiation therapy; HDT, high dose therapy.

Immunohistochemistry

Immunohistochemical staining was performed on pretreatment tumor specimens for CD68; 1.5-mm duplicate cores of diagnostic biopsies of HL were obtained from representative areas containing Hodgkin Reed-Sternberg (HRS) cells. The slides were independently scored by Dr. Young Kim. For CD68 staining, cells were scored in 3 representative high-powered fields, and the relative percentage of $CD68^+$ cells in relation to overall cellularity was reported as previously described [16]. Staining intensity was then assessed for relationship to response rate.

RESULTS

Efficacy

In total, 37 patients were enrolled in the study between August 2011 and May 2014. All patients were assessable for toxicity and efficacy. Table 1 shows baseline patient, disease, and treatment characteristics. All 37 patients were assessable for response. The median number of cycles received was 4 (range, 1 to 4). Table 2 details the ORRs. The ORR was 68% (25/37), with 13 patients attaining CR (35%), 12 patients attaining PR (32%), 10 patients attaining SD (stable disease, 27%), and 2 patient attaining PD (5%). All patients who achieved CR did so after 2 cycles of therapy.

When stratified by stage at diagnosis, the ORR was 68% for stage I/II patients (13/19) and 67% for stage III/IV patients (12/18). When stratified by response to induction therapy, the ORR was 67% for primary refractory disease (16/24) and 69% for relapsed disease (9/13). Univariate analysis did not show significant differences in response rates in terms of age, gender, stage, and response to induction.

Overall, treatment was well tolerated. Table 3 shows all hematologic adverse events, all grades 3 to 4 adverse events, and all grades 1 to 2 nonhematologic adverse events occurring in at least 15% of the patients that were at least possibly related to drug. No patient required growth factor support, packed RBCs, or platelet transfusions as a of result brentuximab vedotin. There were also no neutropenic fevers.

Eighty-six percent of patients (32/37) successfully proceeded to AHCT. Of the 5 not receiving AHCT, 2 went to alloHCT and 3 did not respond to second-salvage combination chemotherapy. Figure 1 shows a flowchart of patient treatment that includes disease response at each step. Seventeen of 37 patients received only brentuximab vedotin (46%) before AHCT. Among the 13 CR patients, all proceeded to AHCT without additional chemotherapy. Among the 12 PR patients, 4 proceeded to AHCT without additional chemotherapy and 8 received additional salvage chemotherapy (ICE/DICE/IGEV/GND). All patients with SD/PD received additional salvage chemotherapy, with the exception of 1 patient who received only local radiation therapy because of a single site of disease. This patient did not have repeat imaging assessment after radiation and thus is counted as a SD. At the time of AHCT, 24 of 37 patients (65%) were in CR, 7 of 37 (19%) were in PR, and 1 of 37 (3%) was in SD.

All 32 patients who underwent AHCT successfully mobilized stem cells. Twenty-one patients were primed for stem cell mobilization with cyclophosphamide and G-CSF per institutional standard of care, and 2 patients received G-CSF only. Nine patients received plerixafor (per standard operating procedures). No patient required a second round of mobilization. The median cell dose collected was 6.0×10^6 CD34 cells (range, 2.6 to 34). The median number of days required for collection was 2 (range, 1 to 6). Patients received AHCT conditioning regimens by physician choice, including BEAM (19/32, BCNU, etoposide, cytarabine, melphalan), CBV (11/32, cyclophosphamide, BCNU, etoposide), or BEAM plus yttrium-90 labeled anti-CD25 (2/32). The median time to neutrophil engraftment (absolute neutrophil count $\geq$ 500 for 3 consecutive days) was 11 days (range 10 to 12) and platelet engraftment ($\geq$20,000) 13 days (range, 9 to 23).

Correlative Assays

CD68 expression has been implicated as a poor prognostic factor in patients undergoing induction chemotherapy [16] and has also been shown to predict for relapses post-AHCT [17]. To determine whether CD68 expression is a poor

Table 1
Patient, Disease, and Treatment Characteristics

Characteristics	Value
Institution	
City of Hope	31 (84%)
Weill Cornell	6 (16%)
Gender	
Female	17 (46%)
Male	20 (54%)
Median age, yr (range)	34 (11-67)
Stage at diagnosis	
I-II	19 (51%)
III-IV	18 (49%)
Prior radiation therapy	9 (25%)
B symptoms (at diagnosis)	23 (62%)
Bulky disease ($\geq$5 cm at diagnosis)	32 (86%)
Induction chemotherapy	
ABVD	34
ABVD/BEACOPP	2
ABVE-PC	1
Prior radiation therapy	9 (24%)
Best response to induction	
Primary refractory	24 (65%)
Relapsed (median 7 months)	13 (35%)

Table 2
Response

	Best Response to Brentuximab Vedotin (n = 37)	Response to Combination Chemotherapy (ICE/DICE/IGEV/GND) after Brentuximab Vedotin (n = 18)	Disease Status at AHCT (n = 33)
ORR	25/37 (68%)	16/18 (89%)	
CR	13/37 (35%)	11/18 (61%)	24/33 (73%)
PR	12/37 (32%)	5/18 (28%)	9/33 (27%)
SD	10/37 (27%)	1/18 (6%)	1/33 (3%)
PD	2/37 (5%)	1/18 (6%)	

Table 3
Adverse Events

Adverse Events	Grade 1	Grade 2	Grade 3	Grade 4
Hematologic				
Anemia	16%	3%		
Neutropenia	11%		5%	
Thrombocytopenia	8%			
Lymphopenia		3%	3%	3%
Nonhematologic				
Peripheral neuropathy	49%	3%		
AST elevation	32%	5%	3%	
ALT elevation	27%	11%		
Rash (new)	24%	11%	5%	
Muscle weakness	24%	5%		
Hypoglycemia	22%			
Fatigue	19%	11%		
Pruritus	19%	3%	3%	
Nausea	16%	3%		
Abdominal pain	11%	5%		
Creatinine elevated			3%	
Tumor lysis syndrome			3%	
Hyperuricemia				3%

AST indicates aspartate aminotransferase; ALT, alanine aminotransferase.

prognostic marker for patients receiving brentuximab vedotin, we performed immunohistochemical staining for CD68 in our patient samples (City of Hope only) before brentuximab vedotin treatment. Not surprisingly, all patients had an intensity score of at least 2 + because they were all either relapsed or refractory to induction chemotherapy. A total of 31% scored as 2+, 62% as 3+, and 6% as 4 + staining intensity for CD68. Fisher's exact test was performed to test for an association between CD68 staining intensity and response to brentuximab vedotin. In our small sample set, it does not appear that CD68 staining intensity negatively impacted the response rates to brentuximab vedotin ($P = .38$). We will continue to follow these patients to determine whether CD68 might be a predictor of relapse post-AHCT in patients who achieved CR to brentuximab vedotin as second-line therapy.

DISCUSSION

The ORR of 68% and CR rate of 35% in this study are similar to the ORR of 75% and CR 34% achieved in the pivotal study of brentuximab vedotin for HL [10]. The toxicity profile was mild and similar to that seen in the post-AHCT brentuximab vedotin trial, with 2 exceptions. Eight percent of patients on the pivotal trial developed grade 3 peripheral neuropathy, whereas none of the patients on this trial developed grade 3/4 peripheral neuropathy. This difference may be related to the brentuximab vedotin 4-dose maximum for patients on our trial, compared with 16 doses in the post-AHCT trial, suggesting that peripheral neuropathy from brentuximab vedotin is a cumulative toxicity. Unlike the pivotal post-AHCT trial, 40% of our patients developed rashes, with 2 patients developing grade 3 rashes. The appearance of this toxicity may be related to the fact that patients in the pivotal trial had received a median of 3.5 prior therapies, whereas patients in the current study had only received 1 induction regimen and were likely better able to mount an immune-mediated skin reaction to the antibody–drug conjugate [10]. The results of our study suggest that brentuximab vedotin has similar activity and tolerability when given in the second-line setting as it has in the setting of post-AHCT failure.

Our results also suggest that brentuximab vedotin as second-line therapy can effectively bridge patients to AHCT. Patients in this study received brentuximab vedotin as second-line therapy, and those who achieved a CR proceeded directly to AHCT. For patients who did not achieve CR, additional combination salvage chemotherapy such as ICE was then given to improve the depth of response before AHCT. This sequential strategy resulted in 13 patients (35%) in CR immediately after brentuximab vedotin and another 11 patients (30%) in CR after salvage chemotherapy, yielding a total of 24 patients (65%) in CR at the time of AHCT. This trial was not designed to replace traditional salvage chemotherapy with brentuximab vedotin but rather to demonstrate that brentuximab vedotin as a second-line therapy can be safely given before traditional salvage chemotherapy to bridge patients to AHCT. Granted, the CR rate of 35% achieved by brentuximab vedotin is lower than the 60% positron emission tomography CR rate seen for ICE [4]. However, the CR rate of multiagent chemotherapy given as third-line therapy is 61% (11/18), suggesting that delaying multiagent chemotherapy does not have a deleterious effect on efficacy.

It is also important to note that 18 patients (49%) proceeded directly to AHCT without multiagent salvage chemotherapy. The toxicity profile for brentuximab vedotin in this trial was milder than that seen for historical control subjects for salvage chemotherapy regimens. Toxicities such as neutropenia, thrombocytopenia, anemia, fever, nausea, vomiting, and mucositis are fairly common in multiagent salvage chemotherapy [3-5]. The initial ICE study resulted in 13% grade 4 neutropenia requiring hospitalization and a 14% stem cell mobilization failure rate [6]. It is important to note that none of the patients in this trial required growth factor support or blood product transfusions as a result of brentuximab vedotin administration. There were also no stem cell mobilization failures in our patients. Brentuximab vedotin did not decrease the median number of stem cells collected or prolong the median number of days required to reach the minimum collection target. The absolute neutrophil count and platelet engraftment times were also similar to historical control subjects. All but 4 patients were able to proceed to AHCT, demonstrating that delaying combination salvage chemotherapy did not negatively impact bridging patients to AHCT.

This study was not designed to predict how this bridging strategy will affect long-term outcomes after AHCT. As secondary endpoints, we continue collecting toxicity profile data and progression-free survival, overall, and relapse rates. However, follow-up is too short for us to draw any conclusions at this point. We do know from prior publications that the best predictor of outcomes for HL patients post-AHCT is CR status before AHCT [4]. Moskowitz et al. [18] recently published a similar trial using weekly brentuximab vedotin followed by augmented ICE before AHCT. They showed that sequential salvage therapy with brentuximab vedotin followed by augmented ICE resulted in a higher proportion of patients achieving CR at the time of AHCT than historically seen for ICE alone. They observed a 2-year event-free survival of 80% after the sequential strategy. Although longer follow-up is needed to determine the survival outcomes of the patients who received AHCT after our sequential strategy, our current results are consistent with the Moskowitz study and support the use of sequential brentuximab vedotin salvage therapy followed by combination chemotherapy before AHCT.

Although the results of this trial support the Moskowitz study in terms of bridging patients to AHCT, there are several differences. First, our brentuximab vedotin dosing schedule was 1.8 mg/kg once every 3 weeks, whereas Moskowitz et al. used 1.2 mg/kg once weekly dosing. Second, we let the individual physician choose the multiagent salvage chemotherapy regimen, given that this was a multicenter study and there are no data on superiority of any 1 particular multiagent chemotherapy regimen. Third, we allowed patients who were in PR after brentuximab vedotin to proceed directly to AHCT without additional therapy, and 4 patients in our trial were transplanted in PR. Although evidence shows improved post-AHCT outcomes for patients in CR at the time of AHCT, there is no guarantee that CR can be achieved with additional therapy before AHCT. Last but not least, we performed rapid restaging after the first 2 doses of brentuximab vedotin. All patients who achieved CR did so by cycle 2, and further dosing with 2 additional cycles did not convert any patients from PR to CR. In the initial pivotal trial, many patients who achieved PR eventually developed PD while still on therapy. Interestingly, 3 of our patients achieved PR by cycle 2 and developed PD later, suggesting that resistance to brentuximab vedotin can develop even after a short exposure. Based on the results of the study presented here, we would recommend giving additional multiagent chemotherapy for patients not in CR after 2 cycles of brentuximab vedotin.

CD68 expression has been implicated as a poor prognostic factor in patients undergoing induction chemotherapy [16] and is also shown to predict for relapse post-AHCT [17]. Although our sample size is small, our data suggest that intensity of CD68 expression did not negatively impact response rates to brentuximab vedotin, at least in the context of a cohort where all patients exhibit at least 2 + staining for CD68. We are currently assessing the expression of drug exporters in our tumor samples, because this class of molecules has been associated with resistance to antimicrotubule agents in other tumor types [17,19,20].

This study demonstrated that brentuximab vedotin as second-line therapy for patients with HL is active, well tolerated, and does not hinder stem cell collection or engraftment. Eighty-six percent of the patients were effectively bridged to AHCT, 49% of which were spared multiagent salvage chemotherapy. This toxicity sparing is particularly important for a patient population that is younger and has many years to live with their treatment toxicities. For HL patients with relapsed/refractory disease after induction chemotherapy, brentuximab vedotin as second-line therapy followed by combination chemotherapy before AHCT can be considered a viable approach.

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